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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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10/700,971

11/04/2003

Muthiah Manoharan

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EXAMINER

MCGARRY, SEAN

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

04/14/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|---|--|
| Office Action Summary | Application No. 10/700,971 | Applicant(s) MANOHARAN ET AL. | |
| | Examiner Sean R. McGarry | Art Unit 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-6,9-13,17,21,24,25,36,37 and 101 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-6,9-13,17,21,24,25,36,37 and 101 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/11/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants response filed 12/18/08 includes the cancellation of claims 2, 3, 7, 8, 14-16, 18-20, 22, 23, 26-35, 38-100, 102 and 103. Claims 1, 9, and 17 have been amended.

Claims 1, 4-6, 9-13, 17, 21, 24, 25, 36, 37, and 101 are pending and under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4-6, 9-13, 17, 21, 24, 25, 36, 37, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al [US 2004/0259247] in view of Beach et al [US2002/0162126] and Manoharan et al [Tetrahedron Letters, Vol. 36(21):3651-3654, 1995].

The claimed invention is as clearly set forth in the claims.

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Tuschl et al have taught the use of siRNA molecules for the inhibition of a desired target nucleic acid. It has been taught that the preferred length of these double stranded RNAs is 19-25 nucleotides. It has been taught at paragraph 15 and 179-181 what positions of an siRNA molecule are important for function and what areas are modifiable such as 5' and 3' ends. It has been taught to use siRNA in cell culture to determine gene function, for example (see paragraphs 28 and 29, for example). Tuschl et al have taught at paragraphs 28-33 that carrier mediated delivery is an option for siRNA introduction into cells. Tuschl et al do not specifically teach conjugate moieties of cholesterol.

Beach et al also teach the use of siRNA and teach that known methods in the art for introducing nucleic acids to cell may be used including lipid-mediated carrier transport (see paragraph 139, for example)

Manoharan et al have taught the use of Lipidic nucleic acids where it has been taught the use of moieties such as cholesterol linked to terminal ends, backbones or bases of antisense oligonucleotides where it is asserted these provide for more efficient antisense administration to cells. It has been taught that attachment at the 2' position of an oligonucleotide should minimize interference with hybridization.

One in the art would clearly combine the teachings of Tuschl, Beach and Manoharan et al to make the instant invention since Tuschl has taught the use of siRNA in cells and Beach has taught that lipid mediated or other known methods of nucleic acid delivery can be used with siRNA. Manoharan provide a teaching of how to make and use lipidic moieties in oligonucleotides for enhanced cellular delivery and Tuschl et

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al have taught locations where siRNAs can be modified. The prior art teaches that the use of such conjugates was known in the art to enhance delivery of nucleic acid into cells, for example. The determination of which strand or both strands to add substituents would clearly have been a matter of optimization as the general use of substituents as claimed was established in the art at the time of invention and Tuschl has provided a clear basis for the locations of modification in a siRNA. The claimed invention appears to amount to the use of a known oligonucleotide delivery method [cholesterol conjugation] and a known oligonucleotide that would be delivered to cells[siRNA].

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 12/18/09 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

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Applicant argues each reference in a vacuum and does not address that art as a whole as presented in the rejection of record.

It is the examiners position that applicants claims are drawn to the combination of known substituents in a fashion that the art suggests. The prior art teaches siRNA and indicates that siRNA can be delivered to cell via known delivery techniques. The art teaches cholesterol conjugation to oligonucleotides for enhanced delivery. Applicant provides no reasons or evidence that the combination is not obvious, but merely indicates that each reference in the rejection does not anticipated the claimed invention. Applicant does not offer that any considerations other than that provided in the art were required to make the claimed invention. Applicant does not offer that there were any unexpected results from the combination of the prior art. Applicants invention appears to be the attachment of a known oligonucleotide to a known oligonucleotide delivery enhancing moiety where the result observed by applicant is enhancement of oligonucleotide delivery.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

/Sean R McGarry/
Primary Examiner, Art Unit 1635